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Subverting the B7-H1/PD-1 Pathway in Advanced Melanoma and Kidney Cancer

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Abstract

Ligands for inhibitory immune receptors on T cells may be constitutively expressed on tumor cells or host cells in tumor microenvironment as a consequence of adaptive immunity. Programmed death 1 (PD-1) is a such receptor on T cells, which functions as a negative regulator of T cell activity. Tumors that up-regulate programmed death ligand 1 (PD-L1) (B7-H1) may abrogate the host's effector T cell antitumor response. Higher tumoral PD-L1 expression has been linked with inferior clinical outcomes. Multiple cancers including renal cell cancers (RCCs) and melanomas have relatively high levels of PD-L1 on the cell surface. Early evaluations of antibodies that block the interaction of PD-1 and PD-L1 have shown efficacy and a favorable tolerability profile with notable inflammatory toxicities that are generally manageable. Upward of 30% of RCC patients and 50% of melanoma patients achieve objective responses. Durable responses can occur, even in some patients who have discontinued treatment. The developing investigation of PD-1/PD-L1 pathway-blocking agents in RCC and melanoma will likely alter our approaches to the treatment of these 2 deadly diseases.

Keywords

PD-1; PD-L1; antibody; melanoma; kidney cancer; renal cell carcinoma; nivolumab; MK-3475; MPDL3280A

Melanoma and renal cell cancer (RCC) have long proven sensitive to immune-modulating agents. Prior to the development of the targeted agents, cytokine-based therapies were integral therapeutic components for both malignancies, albeit with low response rates and considerable toxicities. The last several years have borne out great treatment advances for melanoma with the approval of agents that increase survival including the CTLA-4 antibody

ipilimumab, the BRAF kinase inhibitor, vemurafenib, and combinations that target both the BRAF and MEK pathways such as dabrafenib plus trametinib.¹⁻⁴ Similarly in RCC, improvements in survival have been attained with agents that inhibit the hypoxia-inducible factor and mechanistic (formerly mammalian) target of rapamycin pathways.⁵⁻¹⁶ These targeted therapies are more broadly effective in terms of achieving objective responses and prolonged progression-free survival (PFS) compared with interferon α and high-dose interleukin 2 (IL-2)-based regimens.¹⁷⁻¹⁹ Nevertheless, we have clearly reached a plateau in the ability to improve survival in RCC with these predominantly cytostatic agents. Furthermore, no targeted therapy produces both durable responses and persistent disease control off-therapy like high-dose IL-2 can when it is effective.²⁰ However, these cytokine approaches are variably effective, and no predictors for response have been identified despite intense prospective study. The CTLA-4 blockade story in melanoma suggests that harnessing T cell-mediated processes may be an effective way to treat cancers via manipulation of host immune regulatory elements. Ipilimumab may work both by activating effector T cells and by selectively depleting intratumoral regulatory T cells.²¹ In contrast to CTLA-4, which down-modulates T cell activity earlier in T cell activation,²² targeting the programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway in the tumor microenvironment has shown promising clinical efficacy and less toxicity.

PD-1/PD-L1 PATHWAY RELEVANCE TO RCC AND MELANOMA

Programmed death 1 is a receptor expressed on activated T and B lymphocytes. As a member of the B7-CD28 family of immune modulatory molecules, it regulates T cell antigen-specific signaling and regulates T cell activation, inactivation, and survival.²³ Physiologically, activation of PD-1 negatively regulates the immune response, resulting in tolerance to certain antigens or pathogens with the goal of limiting the autoimmune response and damage to healthy tissues. Interaction with its 2 known ligands, PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD272), results in T cell inhibition, exhaustion, apoptosis, and reduced memory responses.^{24,25}

To circumvent host immunity, tumor cells can express PD-L1 and other immunoinhibitory ligands, which may abrogate the effects of antitumor cytotoxic T cells and block production of important immune-modulating cytokines.^{22,26,27} These ligands may be constitutively expressed on tumor cells or can arise as a consequence of adaptive immunity in response to stressors such as hypoxia, interferon γ secreted by tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment, and treatment with anticancer agents.²⁸⁻³⁴ Approximately 15% to 66% of RCCs and 40% to 100% of melanomas express high levels of PD-L1.^{23,26,35-42} The variability across series may be a result of the definition of PD-L1 “positivity,” tumor heterogeneity, the different diagnostic antibodies used, age of the specimen, and specimen processing.⁴³ Higher expression of PD-L1 by tumor cells and TILs can portend more aggressive tumor behavior and poorer survival.^{23,26,39,40}

In vitro, inhibition of the interaction between PD-1 and PD-L1/PD-L2 potentiates immune responses.^{22,44} To that end, blocking antibodies have been developed with the goal of restoring T cell function and improving outcomes. Several are in clinical development in RCC and melanoma (Table 1). Differences in engineering of the Fc domain of the antibody

can optimize different biologic activities and immune modulation by influencing the degree of antibody-dependent cellular cytotoxicity (ADCC), complement activation, and direct antitumor killing.³⁶ Immunoglobulin G 1 (IgG1) antibodies such as the Curetech compound⁴⁵ optimize direct PD-1+ or PD-L1 + tumor cell killing via ADCC and binding of complement. However, in the process, they may also kill the PD-1+ or PD-L1+ immune effector cells (e.g., TILs) that they restore. Conversely, IgG4 antibodies such as nivolumab and pembrolizumab (MK-3475) have decreased ADCC function and do not bind complement and thus have only minor direct cytotoxicity against the tumor. However, even the minimal ADCC function may kill the induced PD-1 or PD-L1 expressing TILs. To counteract this bystander killing, “effectorless” antibodies have been created, such as the Genentech IgG1 antibody MPDL3280A. These agents have no ADCC or complement-binding function and thus, in theory, may circumvent the elimination of the reinvigorated effector T cells. The 4 PD-1/PD-L1 pathway-blocking agents that have been the best studied in melanoma and RCC include nivolumab, pembrolizumab, MPDL3280, and BMS-936559.

CLINICAL STUDIES OF PD-1 ANTIBODIES IN MELANOMA AND RCC

Nivolumab

Nivolumab is a fully human IgG4 PD-1 antibody. In the initial pilot study, 39 patients with advanced solid tumors were treated at doses of 0.3 to 10 mg/kg with an expansion cohort of 10 mg/kg (NCT00441337).⁴⁶ The antibody was well tolerated, and no maximally tolerated dose (MTD) was identified. No anti-human antibody development was observed. The sole RCC patient who was enrolled developed a partial response.

The second trial was a large phase IB study of 296 solid tumor patients, in which nivolumab was tested at 1, 3, or 10 mg/kg (NCT00730639).⁴⁷ Objective responses were observed in 27% to 28% of melanoma and RCC patients. No MTD was reached and durable responses lasting 1 year or more were attained in 65% of the responders (n = 20/31). Based on the tolerability and preliminary efficacy, an expansion study investigating multiple doses of nivolumab was undertaken in melanoma, RCC, and other solid tumors.

In the RCC expansion cohort, 34 treatment-refractory patients were treated at both the 1- and 10-mg/kg dose levels. Objective response rate was 29%. Median PFS was 7.3 months.⁴⁸ Overall survival (OS) was 70% at 1 year and 50% at 2 years; median survival was greater than 22 months. Median time to response was 8 weeks, and 4 patients had persistent responses at 16 weeks or more off-therapy. These results are especially notable given that many of the patients were heavily pretreated, with 44% having had 3 or more lines of therapy.

In the melanoma dose expansion study, 107 patients with advanced treatment-refractory melanoma received nivolumab at various doses (0.1, 0.3, 1, 3, 10 mg/kg) every 2 weeks.²⁵ The population was advanced, with 62% having had 2 or more prior therapies, 78% with visceral metastases, and 36% with a poor prognostic factor of elevated serum lactate dehydrogenase. Patients with treated brain metastases were permitted. There was no MTD reached across the 2-log range of doses.

When breaking down the efficacy across the dose levels, objective response rate (ORR) ranged from 20% to 41%. Approximately a third had an objective response ($n = 33/107$, 30.8%; 95% confidence interval [CI], 22.4%–40.5). Median duration of response was close to 2 years (104 weeks; range, 24.1–117+ weeks). At the time of the analysis, the majority of responses were ongoing (58%). Responses tended to be fairly rapid, with nearly half occurring by the first tumor assessment at 8 weeks. Sustained and continued responses were observed even off-therapy. In the 17 patients who were responding but discontinued for reasons other than progression, 71% of them had sustained responses or continued disease regression for 16 or more weeks off-therapy (15–56+ weeks). Disease stabilization at 24 weeks or more was achieved in another 7 patients.

In addition to capturing toxicities thought related to the induction of the immune response, another notable difference when assessing the efficacy of these agents is to capture delayed or mixed responses that may be due to immunomodulation rather than the more rapid cytotoxic effects that can be achieved by ADCC or complement binding. Wolchok and colleagues⁴⁹ created a set of “immune response criteria,” which permit integration of new measureable lesions into the total disease burden and initially allow for increased or new disease with the thought that more time may be necessary to mount an immune response or that the growth could be due to increased immune cell infiltration or edema. To allow assessment of this immune or “unconventional” response as a secondary endpoint, most of the early trials with the PD-1/PD-L1 pathway antibodies allowed drug continuation even in the face of radiological disease progression as long as the patient was clinically stable. In the melanoma dose-expansion cohort, unconventional responses, including response following initial progression and persistent reduction in target lesions despite eruption of new lesions, occurred in 4 patients.²⁵

Median PFS was 3.7 months overall but ranged from 1.9 months in the 0.3-mg/kg cohort to 9.1 to 9.7 months in the 1- and 3-mg/kg cohorts, respectively. Given the small numbers, the study was not powered to look at which dose level was the most effective; however, the 10-mg/kg dose did not appear to induce significantly greater efficacy. Furthermore, dose escalation in the 11 patients in the 0.1- and 0.3-mg/kg cohorts who progressed to 1 mg/kg did not induce objective responses. With a minimum of 14 months since treatment initiation and a median time on treatment of 22 weeks (2–122 weeks), the estimated median OS was 16.8 months (95% CI, 12.5–31.6 months). Survival estimates at 1 and 2 years were 62% and 43%, respectively.

The work by Topalian and colleagues²⁵ details the longest follow-up yet reported on patients treated with PD-1 blockade for melanoma. It highlights distinct features that are emerging with this class of agents including durable and ongoing responses even off-therapy, unconventional or delayed immune-induced responses despite the appearance of a new lesion, overall tolerability, and noncumulative toxicity that differentiate this class of agents from traditional chemotherapies or targeted agents. The persistent responses off-therapy for some patients suggest that the mechanism of action is not simply due to blocking the receptor-ligand interaction and restoration of effector T cells, but also by induction of a tumor-specific memory response.²⁵ Although retrospective and with relatively small numbers for a survival analysis, the median OS of 16.8 months compared favorably to

contemporaneous studies of other active agents in melanoma tested in randomized phase II and III studies, such as, ipilimumab (10.1 months) and the selective BRAF and/or MEK inhibitors trametinib and vemurafenib (15.9 months).^{3,4,50} The authors note that the OS far outreaches the PFS and that the OS estimates appear to plateau by 1 year, which is similar to the melanoma experience with ipilimumab.²⁵ It should be noted that PFS might not be the optimal measure of efficacy for agents that induce a delayed immune response. The authors assert that taken together these findings suggest that when using agents that manipulate immune checkpoints, even patients who show early progression may eventually achieve clinical benefit in terms of sustained disease control or even tumor shrinkage. While these results are encouraging, we note that this analysis did not include assessment into the possible confounding effects of subsequent therapies and that phase I trials are fraught with selection bias such that results may not bear out in subsequent randomized trials that are powered to definitively assess time-to-event endpoints.

Delving deeper into the mechanism and potential predictive biomarkers, Weber and colleagues⁵¹ executed a single institution, phase I safety and biomarker study of nivolumab. Various doses (1, 3, or 10 mg/kg) were tested with or without a HLA-A*0201–restricted multipeptide vaccine in 90 advanced stage III or IV unresectable treatment-refractory melanoma patients. The rationale behind giving the vaccine was not necessarily to improve efficacy but to create a platform to evaluate the impact of PD-1/ PD-L1 blockade on antigen-specific T cell responses. Six cohorts of ipilimumab-naïve (n = 34) and -refractory (n = 56) patients were enrolled, and 1 cohort permitted untreated brain metastases. These ipilimumab cohorts were thoughtfully designed with the question of whether the degree of prior ipilimumab immune-related dose-limiting toxicities (DLTs) should be considered when giving subsequent nivolumab; 1 cohort could have only grade 1 or 2 DLTs, whereas the other was required to have had a prior grade 3 DLT related to ipilimumab.

Objective responses occurred in 25% of patients (22/87; 95% CI, 16.6–35.8). Two ipilimumab-naïve patients had a complete response (CR). An additional 18 patients had stable disease at 24 weeks or more (21%). Progression-free survival rate at 24 weeks was 46% and ranged from 39% to 60% in the various cohorts. Responses were seen in both BRAF wild-type and mutant tumors. Although an unplanned analysis, this study also reports one of the first results of sequencing of 2 checkpoint inhibitors. In the ipilimumab-naïve cohorts, 12 of 18 patients who did not respond to nivolumab subsequently received ipilimumab: 2 achieved an objective response, and 2 had mixed response. Overall, this study confirmed that clinical benefit can be achieved in nivolumab-treated patients, even after ipilimumab progression. An important development for the treatment of advanced melanoma is the combination of nivolumab and ipilimumab, which will be described in details in Dr Sznol's article in the issue.

TOXICITY WITH SINGLE-AGENT NIVOLUMAB

No MTD was found in any of the phase I single-agent studies.^{25,46,47,51} The most frequently observed adverse effects (AEs) across the trials were fatigue, rash, diarrhea, and pruritus (Table 2). Adverse effects were generally low grade and reversible. Grade 3–4 treatment-related AEs occurred in 9% to 22% of patients. Of great interest with nivolumab and all

agents blocking this pathway are the so-called immune-related AEs thought induced by immune or inflammatory phenomenon. This class of AEs has been referred to by several names, including “AEs of special interest” and “treatment-related select AEs,” and was observed in 39% to 54% of patients across trials (Table 3). These AEs were frequently low grade and generally consisted of skin disorders (e.g., rash, vitiligo), gastrointestinal disorders (e.g., diarrhea, colitis, transaminitis), endocrinopathies (e.g., hypothyroidism), and pneumonitis. They have been largely manageable with dose holds, hormone replacement, steroids, or immunosuppressive agents (e.g., mycophenolate mofetil, infliximab). Although only a small cohort of 5 patients, the biomarker trial of Weber et al⁵¹ specifically enrolled patients with prior grade 3 immune-related AEs secondary to ipilimumab, and they were not “recapitulated” with nivolumab.

In the longest reported safety follow-up, the authors noted that most AEs tended to occur within the first 6 months and unlike with traditional chemotherapies, prolonged drug exposure did not result in cumulative toxicity²⁵ Pneumonitis is noteworthy with this class of agents. Early in the investigation, there were 3 drug-related deaths due to pneumonitis (2 non-small cell lung cancer, 1 colorectal cancer). While concerning, pneumonitis is also seen with relatively high incidence of up to 15% to 39% with the mechanistic (formerly mammalian) target of rapamycin inhibitors used frequently to treat RCC.^{7,52-54} Albeit preliminary and with no direct comparisons yet resulted, the toxicity profile of nivolumab appears more favorable than the approved targeted therapies in RCC as well as chemotherapy or ipilimumab in melanoma.

Ongoing and Maturing RCC Studies With Nivolumab

Two randomized studies evaluating nivolumab at 0.3, 2, or 10 mg/kg intravenously (IV) every 3 weeks in advanced RCC have completed accrual. The primary endpoint of the efficacy study is to identify the optimal dose based on PFS in 150 patients with advanced RCC who had received prior antiangiogenic therapy (NCT01354431). The biomarker study (n = 90) is evaluating the immunomodulatory activity of nivolumab in both treatment-refractory and -naïve patients at the different doses as characterized by changes in the function and phenotypic characteristics of peripheral immune cells: soluble factors, tumor immune infiltrates, and expression of tumor markers (NCT01358721). The combination of nivolumab plus ipilimumab or targeted therapy is also being investigated in RCC. A 4-arm phase I study has completed accrual and is evaluating nivolumab in combination with sunitinib, pazopanib, or ipilimumab with a primary objective of safety and tolerability (NCT 01472081). The results of these 2 trials will be presented in June 2014. The registration phase III study for nivolumab in treatment refractory RCC has also completed accrual, and data are maturing (NCT01668784). In this trial, 822 patients with clear cell RCC, who have received 1 to 2 prior vascular endothelial growth factor-targeted therapies, were randomized in a 2:1 fashion to either nivolumab 3 mg/kg IV every 2 weeks or everolimus 10 mg daily, with the goal of demonstrating a significant improvement in OS with PD-1 inhibition over the control arm.

PEMBROLIZUMAB (MK-3475, Formerly Known as Lambrolizumab)

Phase I Experience in Solid Tumors

Patnaik and colleagues⁵⁶ detailed the initial experience of MK-3475, a high-affinity humanized IgG4 monoclonal anti-PD-1 antibody in patients with advanced solid tumors using a traditional 3 + 3 phase I design that tested the agent at the 1-, 3-, and 10-mg/kg doses. In the 3 melanoma patients studied, 2 had a confirmed partial response, and 1 had stable disease. No RCC patients were enrolled.

Melanoma Expansion Cohort

Hamid and colleagues reported on the melanoma expansion cohort of the phase I study in 135 patients with advanced melanoma of any type except ocular.⁵⁸ Five cohorts of ipilimumabnaive and -exposed patients including patients with treated brain metastasis were treated at 10 or 2 mg/kg (ipilimumab naive only) every 2 or 3 weeks. The primary endpoint was safety. Nearly 80% of patients had a related AE of any grade, with 13% being grade 3 to 4. The most common toxicities were fatigue, asthenia, fever, chills, myalgias, diarrhea, rash, and pruritus (Table 2). Not surprisingly, the cohort with the highest dose and frequency of administration (10 mg/kg every 2 weeks) had the highest incidence of drug-related AEs. Similar immune-related AEs were observed as with nivolumab (Table 3) with low-grade pneumonitis occurring in 4%.

In terms of efficacy, central review demonstrated an objective response by RECIST (Response Evaluation Criteria In Solid Tumors) in 38% (44/117; 95% CI, 25%–44%). Using investigator-assessed immune-related response criteria, a similar response rate of 37% was observed. This rate increased to 44% if unconfirmed responses were included. The maximum-administered-dose cohort (10 mg/kg every 2 weeks) achieved both the highest toxicity rate but also the highest ORR at 52%. Overall, 77% of patients had some degree of reduction in their tumor burden, and importantly, prior ipilimumab did not influence response rate or degree of toxicity. As in prior studies with antibodies that block the PD-1 axis, responses can be rapid and were seen at the first radiologic assessment at 12 weeks. However, delayed responses or immune-related responses were also observed, with an additional 17 patients achieving objective responses later in the treatment course, one as late as a partial response at 48 weeks on therapy. In keeping with the purported mechanism of action of pembrolizumab, optional biopsies of responding lesions revealed dense infiltrates of CD8+ cytotoxic T cells. Estimated median PFS extended to more than 7 months. At the time of the analysis, median OS had not been reached, and more than 80% of responding patients (n = 42/52) were continuing on study. Given the higher ORR observed at the maximum administered dose of 10 mg/kg but higher toxicity rate as well, a randomized expansion cohort of this study was added to evaluate whether dosing every 3 weeks instead of 2 has equivalent efficacy.

Ongoing or Planned Studies With Pembrolizumab in Melanoma and RCC

Multiple other studies of this agent are ongoing or planned in melanoma. A phase II randomized study evaluating low- or high-dose pembrolizumab versus investigator's choice of chemotherapy (carboplatin + paclitaxel, paclitaxel, dacarbazine, or temozolomide) in

patients whose disease is refractory to ipilimumab or a BRAF/ MEK inhibitor has completed accrual (n = 510, NCT01704287). Another accrued randomized study is evaluating 2 dosing schedules of pembrolizumab 10 mg/kg IV every 2 versus 3 weeks compared with ipilimumab with coprimary endpoints of OS and PFS (n = 645, NCT01866319). An expanded access program for patients with metastatic melanoma, who have failed prior ipilimumab or a BRAF/MEK inhibitor, is ongoing (NCT 02083484). A phase I/II safety and tolerability study of pembrolizumab plus pegylated interferon alfa-2b or pembrolizumab plus ipilimumab in patients with advanced melanoma or RCC has recently opened (MK-3475-029, n = 345, NCT02089685). The phase II portion of that study will randomize patients to either of the combinations or to pembrolizumab monotherapy. In RCC, an ongoing phase I/II study is assessing the safety and efficacy of pembrolizumab in combination with pazopanib in advanced treatment-naïve, clear cell RCC (n = 228, NCT02014636). The initial phase will be a traditional 3 + 3 dose escalation design followed by an expansion cohort. The phase II portion is a randomized 3-arm design, which will compare whether the combination increases PFS compared with either single-agent pembrolizumab or pazopanib.

CLINICAL STUDIES OF PD-L1 ANTIBODIES IN MELANOMA AND RCC

MPDL3280A

Genentech's engineered effectorless IgG1 PD-L1 antibody, MPDL3280A, was studied in the phase II setting in 140 patients with incurable, unresectable, metastatic solid tumors (NCT01375842). After an accelerated dose escalation at lower doses ranging from 0.01 to 0.1 mg/kg, an MTD was not observed at higher doses of 0.3, 1, 10, and 20 mg/kg IV every 3 weeks. Expansion cohorts of RCC and melanoma patients were enrolled at the 10-, 15-, and 20-mg/kg doses. Treatment beyond progression was permitted in the hopes of a delayed immune response.

In the RCC expansion cohort of 55 treatment-naïve and -refractory patients, no MTD or DLTs were observed.⁵⁹ The majority of AEs were low grade with 13% of grade 3 to 4 AEs deemed treatment related (Table 2). No grade 3/4 pneumonitis, colitis, or immune-related AEs were observed (Table 3). Objective responses were seen in 13% of RCC patients (n = 47), 13% of clear cell patients, and 17% of the non-clear cell patients. An additional 32% of patients had stable disease for 24 weeks or longer, resulting in a 24-week PFS rate of 53%. Like with other PD-1 axis-blocking agents, responses could rapid, could be seen even after development of new lesions (so called gradual, mixed, or immune-mediated responses), and tended to be durable.

The melanoma expansion cohort of 44 patients permitted all histologic subtypes and treatment-naïve patients (39%).⁵⁹ The AE spectrum was similar to that seen in the RCC cohort with no MTD, DLTs, pneumonitis, colitis, or treatment-related deaths (Table 2). Objective responses were observed in 29%. An additional 5% achieved stable disease for at least 24 weeks for a 24-week PFS rate of 43%. Disease control was not achieved in the poor-prognosis ocular melanoma patients.

Programmed death ligand 1 expression may increase after treatment with targeted therapies.^{29,31,34,59} Given data that vemurafenib or exposure to BRAF inhibitors induces T cell infiltration, antigen expression, and PD-L1 expression on tumors,^{29,31,59} a phase Ib study is investigating the combination of MPDL3280A with vemurafenib in 44 treatment-naïve BRAF-mutant melanoma patients (NCT01656642). One CR has been seen in the first cohort (n = 3).⁵⁹ In treatment-naïve RCC, a phase II study is seeking to improve PFS with MPDL3280A in combination with bevacizumab compared with MPDL3280A alone or sunitinib (n = 150, NCT01984242).

BMS-936559

The IgG4 PD-L1 antibody, BMS-936559, was evaluated in a large 207-patient phase I solid tumor study that included 55 patients with advanced treatment-refractory unresectable melanoma and 17 with RCC.²² In a dose-escalating manner, patients received BMS-936559 0.3, 1, 3, or 10 mg/kg every 2 weeks. The MTD was not reached. Overall, the drug was well tolerated. Most AEs were low grade, with only 9% being grade 3 or 4 (Table 2). Only 6% of patients discontinued treatment because of drug-related AEs. With the exception of no pneumonitis, similar immune-mediated AEs that have been observed with the other PD-1 pathway-blocking agents were reported in 39% (Table 3).

Except for the lowest dose explored, antitumor activity was seen at all doses. In the 52 melanoma patients, 17% achieved an objective response including 3 CRs. In 5 of the 9 responders, responses lasted greater than 1 year. An additional 27% (n = 14) had disease stabilization at 6 months or more. In RCC, 12% of patients experienced objective responses, all at the highest dose level of 10 mg/kg. No CRs were achieved, but an additional 41% achieved disease stabilization for at least 24 weeks, resulting in an overall clinical benefit rate of 68% and a 24-week PFS of 53%.

Overall, BMS-936559 was tolerable and achieved prolonged tumor regression and disease stabilization across a spectrum of solid tumors. However, and although not directly compared with nivolumab, the phase I trials were companion studies executed and resulted at the same time. Given the lower frequency of objective responses, this drug has not been developed further in cancer. A study in HIV is planned but not yet recruiting.

FUTURE DIRECTIONS

Three major areas for future exploration of these agents include investigation of rational combinations with other targeted therapies or immunomodulatory agents, application of the strategy earlier in the disease state, and identification of predictive biomarkers that will enhance selection choice for patients.

Changing Treatment Paradigms in Nonmetastatic Disease

Capitalizing on the early but promising activity of PD-1/ PD-L1-blocking antibodies in metastatic disease, one can envision incorporating this strategy earlier in the perioperative setting to permit further elucidation of their mechanisms of action, optimize their use, and ideally enhance cure rates in earlier-stage disease. Preliminary data from animal models suggest that the tumor-specific CD8+ T cells reside mostly in the primary tumor and the

tumor-draining lymph nodes.^{60,61} (Fig. 1) Thus, a radical nephrectomy is likely to remove the majority of these tumor-specific effector cells, which could result in a diminished response to PD-1/PD-L1 antibody administration if given only after tumor resection, that is, in a purely adjuvant setting. Recent clinical data support this notion; patients with RCC have elevated levels of PD-1, which gradually return to normal after nephrectomy,⁶² raising the question as to where one would expect anti-PD-1 to bind in the adjuvant setting. In contrast, neoadjuvant treatment would be expected to augment an antitumor immune response by expanding the patient's endogenous tumor-specific PD-1-expressing cells to infiltrate the primary tumor and tumor-draining lymph nodes. In addition, the array of effector cells expanded by anti-PD-1 would further be expected to traffic to distant sites as effector memory cells, escape surgical removal, and potentially eradicate micrometastatic disease. Finally, in the absence of tolerizing antigen, the anti-PD-1-activated T cells may progress toward a central memory phenotype, which is more refractory to tolerance and longer living and has more anticancer activity.⁶⁰ Thus, an argument can also be made for postoperative, adjuvant treatment (preceded by a short neoadjuvant course) to promote continued expansion of these effector cells and control or eradicate micrometastases, which account for the 30% to 50% of patients who relapse after resection. By combining surgical resection with PD-1/PD-L1 blockade-mediated augmentation of an antitumor immune response, this strategy could translate to improved disease control and survival in all stages, but with its highest potential to eliminate micrometastatic disease and increase cure in early-stage disease. In RCC, several trials embodying these concepts are under development by investigators in the Eastern Cooperative Oncology Group Genitourinary Committee; these trials will investigate the strategy of harnessing the patient's immune system by targeting a reasonably well-characterized tumoral escape mechanism.

PREDICTIVE BIOMARKERS

No biomarker has been identified that precisely selects patients who will achieve the most benefit from PD-1 blockade. Tumoral PD-L1 expression, soluble PD-L1, and TILs are potential predictive readouts. The marker that has been studied most extensively is tumoral PD-L1 expression; however, results have been conflicting (Table 4). In the early-phase studies of solid tumors, RCC, and melanoma, only a selection of patients had tumor tissue available, and PD-L1 expression of 5% or greater ranged from 27% to 60%. Combining the results across the published studies, it appears that higher baseline PD-L1 tumor expression (1%–5%) does seem to predict for a higher chance of responding, but it does not ensure response, nor does lack of expression or lower expression equate to inability to respond to these agents. Thus, use of PD-L1 as a predictive biomarker is an area of active investigation requiring further refinement, validation, and development of accurate expression assays. Issues that may thwart the use of this modality are defining the optimal positivity cutoff, tumor heterogeneity,^{63,64} variability and impact of tissue processing (e.g., fresh or frozen paraffin embed-ded),⁴³ age of the specimen,⁴³ and the likely dynamic nature of PD-L1 expression on tumors based on both adaptive and intrinsic mechanisms.^{32,33}

CONCLUSIONS

In summary, the PD-1/PD-L1 blockade is a promising and emerging therapeutic strategy in melanoma and RCC. Preliminary data demonstrate that the available antibodies can be effective and tolerable with a manageable toxicity profile. While the maturing registration trials will definitively assess their efficacy, these agents are especially notable for their ability to induce both rapid and delayed immune-mediated responses as well as sustained responses off-therapy. Rational future directions for investigation include building on the proven efficacy of the approved targeted therapies and strategies to enhance the immune response by cotargeting other immune suppressive molecules (e.g., LAG-3, TIM-3) or combining with costimulating molecules or vaccines.

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FIGURE 1.

Preliminary data from animal models suggest that the tumor-specific CD8+ T cells reside mostly in the primary tumor and the tumor-draining lymph nodes. Adapted from www.mcnealisworks.com/illustrations/kidney with permission from artist Alexandra McNealis.

TABLE 1

PD-1/PD-L1–Blocking Agents in Development in Melanoma and RCC

Agent	Antibody/Molecule Type	ORR RCC	ORR Melanoma	Level of Development
Nivolumab (BMS-936558) ^{25,48,51}	Fully human IgG4 PD-1 Ab	29%	25%–31%	Phase III studies maturing
Pembrolizumab (MK-3475, lambrolizumab, Merck) ⁵⁷	Humanized IgG4 PD-1 Ab	NR	47%	Phase II
MPDL-3280A (Genentech) ^{58,59}	Fully human PD-L1 mutated IgG1 Ab (effectorless)	13%	29%	Phase II
BMS-936559 ²²	Fully human PD-L1 IgG4 Ab	12%	17%	Not being developed in oncology currently
CT-011 (Curetech) ⁴⁵	Humanized PD-1 IgG1 Ab	NR	NR	Phase I in solid tumors accrued Vaccine study in RCC ongoing
Medi-4736 (Medimmune)	Fully human PD-L1 IgG4 Ab	NE	NE	Phase I mono therapy and combination studies ongoing
AMP-224 ⁶⁵ (Amplimmune)	PD-L2 (B7-DC-FC) IgG1 fusion protein	NR	NR	Phase I accrued

NE, not yet evaluable; NR, not reported.

TABLE 2

Anti-PD-1/PD-L1 Antibodies Most Frequently Observed or Notable Drug-Related* AEs

AE	Nivolumab ^{25,47,55}	Pembrolizumab ^{56,57}	MPDL3280A ^{58,59}	BMS-936559 ²²
Any	70%–84%	47%–79%	NR	61%
Drug-related grade 3 or 4	14%–22%	13%	13%–14%	9%
Drug-related severe AEs	11%–21%	NR	NR	5%
Tx d/c due to AEs	5%–9%	NR	NR	6%
Fatigue	9%–32%	12%–30%	35%–59%	16%
Rash	9%–23%	21%	16%–20%	7%–9%
Diarrhea	9%–18%	6%–20%	22%–30%	9%
Pruritus	10%–18%	21%–24%	25%	6%
Decreased appetite/anorexia	3%–8%	4%	18%–21%	3%
Nausea	3%–8%	10%–12%	20%–23%	6%
Elevated lipase	12%	NR	NR	NR
Fever/pyrexia	1%–5%	7%	21%–26%	3%
Chills	NR	7%	16%–18%	1%
Asthenia	NR	10%	NR	NR
Infusion reactions	2%–6%	NR	NR	10%
Arthralgia	3%–7%	15%	16%–33%	7%
Cough	3%–6%	8%	21%–27%	NR
Constipation	NR	3%	21%–22%	NR
Back pain	NR	2%	18%	NR
Dyspnea	NR	4%	18%–23%	NR
Headache	3%	10%	16%–32%	9%

* With the exception of the MPDL3280A data, the AEs are treatment related. Thus, the higher percentages in the MPDL3280A data in part reflect reporting of both related and unrelated AEs.

d/c Indicates discontinuation; NR, not reported; Rel, related; Tx, treatment.

TABLE 3

Immune-Related or AEs of Special Interest

AE	Nivolumab ^{25,46,37,55}	Pembrolizumab ^{56,57}	MPDL3280A ^{*58,59}	BMS-936559 ²²
Any	41%–54%	NR	NR	39%
Drug-related grade 3 or 4 immune AE	5%–6%	NR	5%	NR
Tx d/c due to Immune AEs	9%	NR	NR	NR
Skin disorders	9%–36%			7%
Vi ti ligo	3%–9%	9%		2%
Rash	9%–23%	21%	16%–20%	7%–9%
Pruritus	10%–18%	21%–24%	25%	6%
Pneumonitis	2%–3% any grade 1% grade 3/4 3 deaths	4%–6% grade 1/2	0%	0%
Gastrointestinal events	18%			
Colitis	2%		0%	
Diarrhea	9%–18%	20%		9%
Hepatitis	1%			
Transaminitis	3%–6%	8%–17%	16%	1%
Endocrinopathies	6%–13%	8%	NR	
Hypothyroidism	3%–6%			3%
Hyperthyroidism	2%–6%			3%
Adrenal insufficiency	1%–3%			1%
Hypophysitis	3%			1%

* Includes both related and unrelated AEs.

d/c Indicates discontinuation; NR, not reported; Rel, related; Tx, treatment.

TABLE 4
Summary of PD-L1 Expression and Correlation With Objective Responses in the RCC and Melanoma Trials

Tumor Type	Agent	No. With Tissue	Definition of PD-L1+ [*]	% PD-L1+ (n)	ORR PD-L1+ (n)	ORR PD-L1- (n)	IHC Antibody/Miscellaneous
Brahmer et al ⁴⁶	Nivolumab	9	5%	44% (4/9)	75% (3/4)	0% (0/5)	L. Chen [‡]
Topalian et al ⁴⁷	Nivolumab	42 (5 RCC, 18 melanoma)	5%	60% (25/42)	36% (9/25)	0% (0/17)	L. Chen [‡]
Cho et al ⁵⁸	MPDL3280A	31	5%	33% (10/31)	20% (2/10)	10% (2/21)	Genentech Ab
Hamid et al ⁵⁹	MPDL3280A	38	5%	39% (15/38)	27% (4/15)	20% (3/15)	Genentech Ab
Weber et al ⁵¹	Nivolumab	44	>5%	27% (12/44)	67% [‡] (8/12)	19% (6/32)	$P = 0.004$
			>1%	54% (23/44)	39% (9/23)	23% (5/21)	
Wolchok et al ⁵⁵	Nivolumab + ipilimumab	56	5%	38% (21/56)			Clone 28-8 [§]
				Concurrent	46% (6/13)	41% (9/22)	$P > 0.99$, NSS
				Sequential	50% (4/8)	8% (1/13)	

^{*} PD-L1 testing was generally done on the tumor cells with the exception of MPDL3280A in which case the investigators reported the PD-L1 positivity of the tumor infiltrating immune cells.

[‡] Murine anti-human B7-H1 (PD-L1) monoclonal antibody clone 5H1.

[‡] Statistically significant.

[§] Rabbit monoclonal anti-human PD-L1 antibody known as clone 28-8 and Dako's automated assay.

Ab indicates antibody; IHC, immunohistochemistry; NSS, not statistically significant.